American Journal of Transplantation 2014; 14: 2412–2416
Wiley Periodicals Inc.

doi: 10.1111/ajt.12856

Case Report

Combined Liver and Lung Transplantation With Extended Normothermic Lung Preservation in a Patient With End-Stage Emphysema Complicated by Drug-Induced Acute Liver Failure

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Isolated lung transplantation (LuTx) and liver transplantation are established treatments for irreversible lung and liver failure. Combined liver and lung transplantation (cLiLuTx) is a less common, but approved therapy of combined organ failure, mostly applied in patients suffering from progressive cystic fibrosis and advanced liver disease. We report a patient who was listed for LuTx due to end-stage chronic obstructive pulmonary disease and who developed drug-induced acute hepatic failure. The only therapeutic option was hyper-urgent cLiLuTx. To correct the poor coagulation in order to reduce the per-operative risk of bleeding, the liver was transplanted first. In anticipation of the longer lung preservation time, cold flushed lungs were preserved on a portable lung perfusion device for *ex vivo* normothermic perfusion for 11 h 15 min, transplanted sequentially off-pump, and reperfused after a total *ex vivo* time of 13 h 32 min and 16 h for the first and second lung, respectively. Ten months later, the patient is doing well and no rejection occurred. Normothermic *ex vivo* lung perfusion may help to prolong preservation time, facilitating long-distance transport and combined organ transplantation.

Abbreviations: cLiLuTx, combined liver and lung transplantation; cLiThTx, combined liver and thoracic transplantation; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; ET, Eurotransplant; EVLP, *ex vivo* lung perfusion; FEV_1, forced expiratory volume in 1 s; HU, hyper-urgent; INR, international normalized ratio; LiTx, liver transplantation; LuTx, lung transplantation

Received 03 March 2014, revised 20 May 2014 and accepted for publication 31 May 2014

Introduction

Lung transplantation (LuTx) remains the ultimate therapeutic option in selected patients with end-stage respiratory insufficiency. Several underlying lung diseases are also prone to develop hepatic complications. Most frequent diseases with dual organ failure are cystic fibrosis and α1-antitrypsin deficiency. On the other hand, patients with end-stage liver cirrhosis, who have developed treatment-resistant porto-pulmonary hypertension are not amenable to isolated liver transplantation (LiTx) because of the associated morbidity and mortality that pulmonary hypertension entails (1). To date, reports on combined liver and lung transplantation (cLiLuTx) are scarce (2). We report on a patient, primarily referred with end-stage chronic obstructive pulmonary disease (COPD) and listed for bilateral LuTx, who developed drug-induced acute liver failure. The only remaining life-saving therapy was cLiLuTx.

Case Report

A 62-year-old female (blood group: A^-, cytomegalovirus [CMV]: +, weight: 50 kg, length: 1 m and 60 cm) was listed for bilateral (sequential single) LuTx as a consequence of end-stage respiratory failure due to COPD GOLD IV (forced expiratory volume in 1 s [FEV_1]: 31%; DLCO: 27%; BODE

index: 7) with clear evidence of emphysema on computed tomography. During pretransplant work-up (03/2013), 4 months prior to transplantation, the patient was initiated on isoniazid (250 mg/day) because of suspicion of latent tuberculosis infection (IGRA: +, intradermal test: −). In addition to this, and in order to limit the frequence of infectious COPD exacerbations, the macrolide antibiotic roxithromycin (150 mg; 3×/week) was prescribed. Four months later (07/2013), and 2 weeks after increasing the intake of roxithromycin (150 mg/day), the patient suddenly developed anorexia and jaundice, and was urgently admitted with acute hepatic failure (bilirubin: 21 mg/dL, aspartate transaminase: 3732 U/L, international normalized ratio [INR]: 1.9). Diagnosis of isoniazid (and possibly roxithromycin)-induced acute liver failure (progressively worsening encephalopathy and increasing INR $>$ 10) was made and intubation was inevitable. Only remaining options were either therapeutic de-escalation or hyper-urgent (HU) cLiLuTx. After thorough multidisciplinary evaluation, a request for HU cLiLuTx was sent to Eurotransplant (ET). HU LiTx listing was granted immediately since the patient fulfilled King's College criteria. After rebuttal, ET thoracic auditing committee granted listing for simultaneous HU LuTx. Four days later, a liver graft and bilateral lung grafts were procured from a 40-year-old male donor who died from an intracranial bleeding (blood group: O^+; CMV: +, weight: 55 kg, length: 1 m and 68 cm). As a consequence of severe coagulation disorder in the recipient and the suspected risk of bleeding during LuTx, it was agreed to transplant the liver first, while pulmonary grafts were preserved during normothermic *ex vivo* lung perfusion (EVLP; Figure 1). The liver was preserved with 4 L of University of Wisconsin (UW) solution (Viaspan®, Du Pont, Wilmington, DE) and stored on ice. The lungs were flushed and cooled with 3 L of Perfadex® (XVIVO, Göteborg, Sweden [formerly named Vitrolife]), connected to the Organ Care System (OCS™) Lung device (Transmedics, Andover, MA), perfused with 2 L OCS™ solution mixed with 4 U of packed red blood cells, and rewarmed to 37°C. Transport time was 4 h 27 min. The liver was transplanted orthotopically with veno-venous bypass and reperfused after 5 h 20 min of cold and 32 min of warm ischemia. Total operative time for LiTx was 6 h 29 min. The lung procedure was started 1 h 36 min after finishing the LiTx. The INR at that moment was 1.3. Lungs were perfused on the portable lung perfusion device for 11 h 15 min with stable mean pulmonary artery and peak airway pressures (Figure 2). After a second cold Perfadex® flush, the first (left) and second (right) lung were implanted sequentially off-pump through bilateral anterior thoracotomy and reperfused after a total *ex vivo* time of 13 h 32 min and 16 h (including 2 h 17 min and 4 h 45 min cold ischemia), respectively. Total operative time for LuTx was 6 h 29 min. Postoperatively, the patient regained consciousness upon improved liver function, was extubated on day 7, discharged from intensive care unit on day 12 and from hospital on day 60 after rehabilitation due to steroid-induced myopathy. Immunosuppression was administered according to our lung transplant protocol. Induction immunosuppressive therapy consisted of 1000 mg intravenous mycophenolate mofetil, 3 days of rabbit antithymocyte globulin (3 mg/kg/day) and 3 × 125 mg methylprednisolone during the first postoperative day. Maintenance therapy consisted of tacrolimus with a target trough-level of 12 ng/mL, mycophenolate mofetil (1000 mg; 2×/day) and a steroid taper (starting at 0.4 mg/kg/day from day 2).

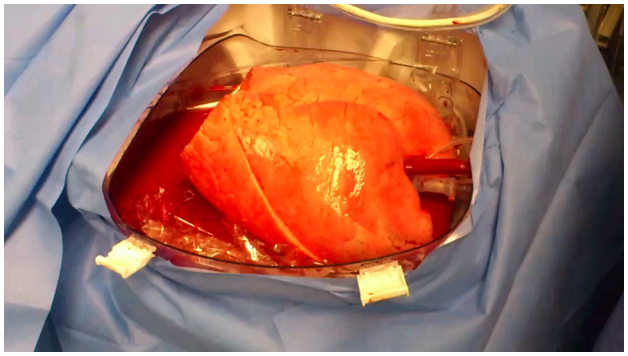

Figure 1: Clinical *ex vivo* lung perfusion on the portable OCS™ Lung perfusion device.

Four months posttransplant, mild cholestasis was noticed during routine check-up (gamma-glutamyltransferase: 262; alanine aminotransferase: 320 U/L, bilirubin: 0.64 mg/dL) and subsequent magnetic resonance cholangio-pancreaticography revealed an ischemic stenosis of the common bile duct anastomosis. The stricture was successfully stented by endoscopic retrograde cholangio-pancreaticography. During 10 months follow-up, no rejection of the liver or lung allograft has occurred and pulmonary function has been excellent with a most recent predicted FEV_1 of 94%.

Discussion

The limited clinical series in literature illustrate that cLiLuTx is a viable and justifiable treatment option for selected patients with either end-stage lung and advanced liver disease, or in patients with end-stage liver disease and secondarily compromised respiratory function (2).

Allocation rules for simultaneous organ transplantation in Belgium are based on ET regulations: (1) Patients are listed after the HU requests and (2) allocation of thoracic organs precedes the liver, intestine, pancreas and kidneys. This implicates that for cLiLuTx the lung allocation rules will be followed (center-oriented allocation of lungs from local donors within the hospital network). At our center, we have experience with nine cases of combined liver and thoracic transplantation with a median time on the waiting list of 72 days. The only HU request within this series is the currently reported case, describing a sudden onset of drug-induced

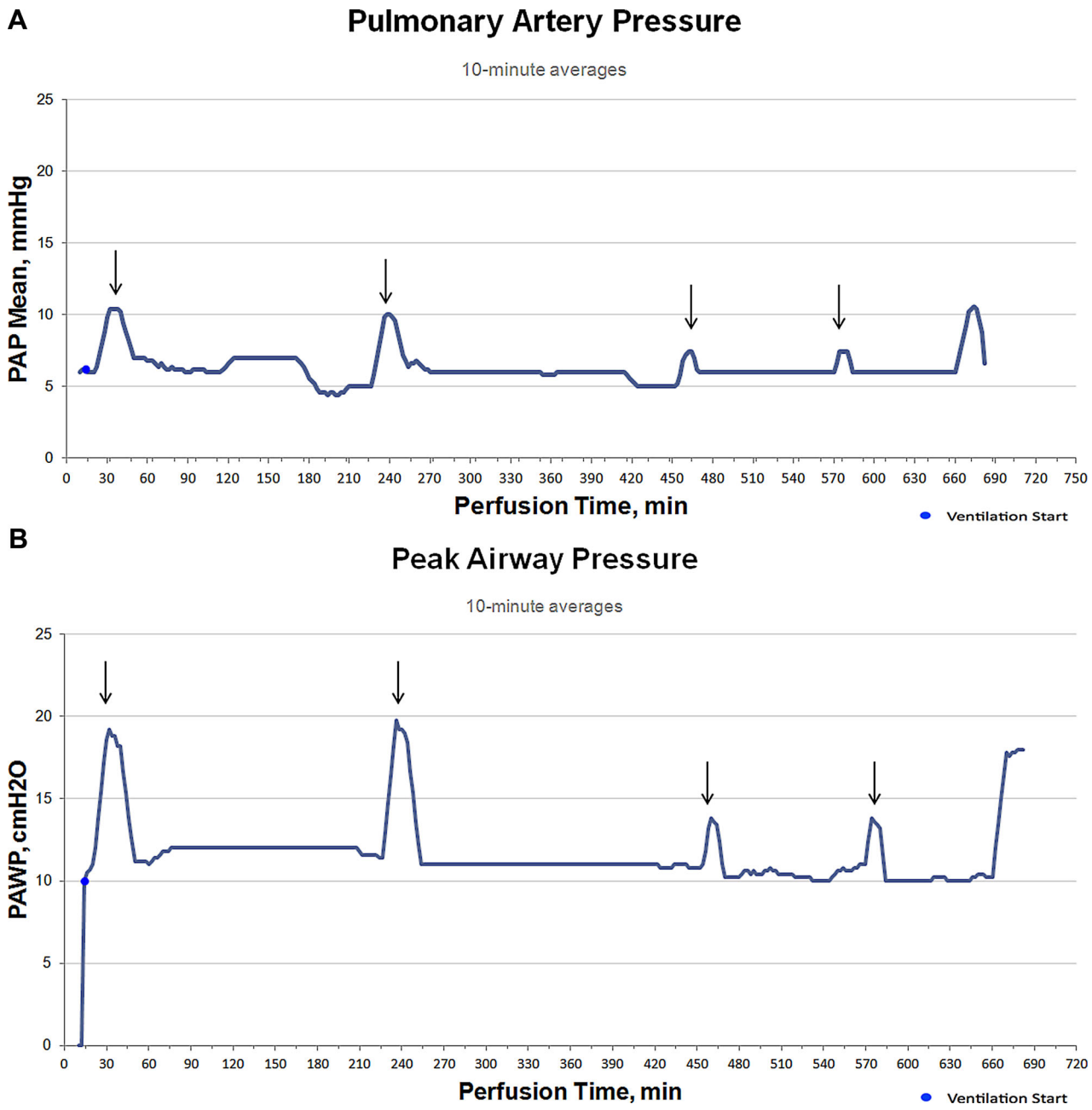

Figure 2: Gradient for pulmonary artery pressure (A) and peak airway pressure (B) remained stable during 11 h 15 min of normothermic *ex vivo* lung perfusion (EVLP). The arrows indicate moments of alveolar recruitment on the device with higher positive end-expiratory pressure (7 cm H_2O) and oxygen concentration (21%) in the bronchoscopy mode setting of the ventilator.

acute liver failure. According to the literature, isoniazid is the most common cause of tuberculostatic-induced hepatic failure (3). Although the patient was administered isoniazid for several months, the acute liver failure presented only 2 weeks after the increase of the roxithromycin intake. The relation of the latter to fulminant hepatic failure is less well documented (4,5). Easton-Carter et al (4) described a case of a healthy 5-year-old boy who developed a generalized jaundice, after a 5-day course of roxithromycin (50 mg; 2×/day). Laboratory results revealed acute hepatic failure and 9 days later, the boy had to be transplanted. In case of rapidly progressing liver failure and encephalopathy, LiTx remains the only rescue therapy.

The additional respiratory failure confronted our patient with a very high risk situation. It was felt that after an

isolated LiTx, it would be very difficult to wean this end-stage COPD patient from mechanical ventilation, jeopardizing the outcome. Therefore, it was agreed that cLiLuTx was the only possible life-saving therapeutic option. Since the risk of severe bleeding during LuTx was almost inevitable due to the abnormal coagulation status, the decision was made to prioritize the LiTx. In that way, the coagulation status could be corrected and subsequent LuTx was deemed to be safer.

To the best of our knowledge, this reversed transplant procedure with the liver first has not been described. An additional theoretical advantage of this sequence might be the immunological protective effect that the liver may exert on the lung graft. Since the first observation by Sir R. Calne, this phenomenon has been attributed to different mechanisms, such as microchimerism, immune diversion or creation of an antigen ''sink'' in which the liver diverts the immune system away from the co-transplanted organ, immune paralysis due to high antigen loads, and partial tolerance induced by the liver's ability to release soluble class I antigens (6,7). This intriguing effect was illustrated in a report by Daly et al (8) in a 50-year-old female suffering from end-stage heart failure in combination with liver cirrhosis and a high titer of HLA antibodies and panel reactive antibodies (98%). It was hypothesized that desensitization protocols would be insufficient and based on the reported desensitizing effect of combined liver–kidney transplantation in case of highly immunized patients, the liver was transplanted first (9). Cardiac ischemic time could be minimized to 4 h 17 min. After transplantation cross-match turned negative and anti-HLA antibody titers decreased significantly. No rejection was shown in the first 15 months posttransplant.

In contrast to the heart, the tolerable ischemic time for the lung is longer and therefore it could be assumed that the transplant sequence in cLiLuTx could be safely inversed. In fact, the first report on clinical EVLP by Steen et al (10) in 2001 described a total ischemic time for the lung of almost 13 h 30 min. The same team described in 2007 a total *ex vivo* time of 17 h for an initially nonacceptable donor lung in which 6 h 30 min of topical cooling and reconditioning with normothermic perfusion were followed by 10 h 30 min of so-called topical ECMO at 8°C (11). However, acceptable lung ischemic time in Leuven is limited to 8–10 h and since a longer time was anticipated, the lungs were normothermically perfused and preserved. Based on our previous experience with the portable lung perfusion device in the *Inspire* trial (12,13), it was considered that normothermic EVLP would limit the cold ischemic injury and could prolong *ex vivo* preservation. Review of the literature revealed that 11 h 15 min of clinical EVLP in our case is the longest reported (14). Experimental studies have shown that EVLP was safe and feasible for even longer periods. The Toronto group assessed porcine lungs for 12 h EVLP and demonstrated that (i) donor lungs could be maintained without inflicting significant added injury (15) and (ii) ongoing lung injury was prevented during 12 h EVLP when compared to a cold storage control group (16).

The rationale of EVLP is to keep the lungs in a physiological state which allows the pulmonary cells to remain metabolically active and viable for several hours. This period provides a window for assessment and reconditioning of previously unacceptable grafts, thereby enlarging the donor pool as recently demonstrated in several clinical series (17–20). The reconditioning can be attributed to several mechanisms: dehydration by the high oncotic pressure in the perfusate, removal of blood clots and inflammatory cytokines with filters and recruitment of atelectatic areas (14). Results from an ongoing clinical study (*Inspire* trial) comparing cold storage with normothermic perfusion are awaited to determine if extended normothermic EVLP is safe and superior to cold storage (12). If this would be demonstrated, new avenues could be opened to preserve and recondition lungs for a longer period of time. Until then, cold storage remains the gold standard for lung preservation.

In conclusion, four unique aspects are illustrated in this case: (1) Isoniazid is a rare cause of acute liver failure and indication for HU LiTx. In this patient, roxithromycin may also have exerted a role. (2) Acute liver failure developed in an already actively listed LuTx candidate, rendering isolated LiTx probably futile and making HU cLiLuTx the only option. (3) To correct the poor coagulation, LiTx was performed prior to LuTx. (4) Clinical prolonged normothermic EVLP for 11 h is feasible. This technique may help to prolong preservation time facilitating long-distance transport and combined organ transplantation.

Acknowledgments

The authors wish to thank and recognize the tremendous clinical efforts of their colleagues, who were involved in this case: A. Wilmer, G. Hermans (Medical Intensive Care); R. Dreelinck, G. Poortmans, M. De Cang, E. Dierickx (Anaesthesiology); N. Meurisse, T. Verbelen, S. Strypstein (Abdominal Transplant Surgery); L. Depypere (Thoracic Surgery), P. Bomans, L. Dupont, M. Delcroix (Pneumology); M. Schetz, D. Mesotten (Intensive Care Medicine); B. Desschans (Transplant Coordination).

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. DM and JP are holders of a chair in Abdominal Transplant Surgery from the Centrale Afdeling voor Fractionering (CAF), Vilvoorde, Belgium. WL, SvdM and FN are senior clinical investigators supported by the Fund for Research Flanders, Belgium (FWO). RV is supported by the FWO (KAN2014 1.5.139.14) and Clinical Research Fund (KOF) at the University Hospitals Leuven, Belgium. GV is supported by the Glaxo Smith Kline (Belgium) Chair in Respiratory Pharmacology at the KU Leuven, grants from

the FWO (G.0723.10, G.0753.10, G.0679.12 and G.0705.12) and a grant from the KU Leuven, Belgium (OT10/050). DVR is a consultant for *Transmedics* (Andover, MA) and is a senior clinical investigator supported by the FWO (G.3C04.99) and a grant from the KU Leuven, Belgium (OT/11/079).

References

1. Pirenne J, Verleden G, Nevens F, et al. Combined liver and (heart-) lung transplantation in liver transplant candidates with refractory portopulmonary hypertension. Transplantation 2002; 73: 140–156.
2. Yi SG, Burroughs SG, Loebe M, et al. Combined lung and liver transplantation: Analysis of a single-center experience. Liver Transpl 2014; 20: 46–53.
3. Ichai P, Saliba F, Antoun F, et al. Acute liver failure due to antitubercular therapy: Strategy for antitubercular treatment before and after liver transplantation. Liver Transpl 2010; 16: 1136–1146.
4. Easton-Carter KL, Hardikar W, Smith AL. Possible roxithromycin-induced fulminant hepatic failure in a child. Pharmacotherapy 2001; 21: 867–870.
5. Pedersen FM, Bathum L, Fenger C. Acute hepatitis and roxithromycin. Lancet 1993; 341: 251–252.
6. Calne RY, Sells RA, Pena JR, et al. Induction of immunological tolerance by porcine liver allografts. Nature 1969; 223: 472–476.
7. Rana A, Robles S, Russo MJ, et al. The combined organ effect: Protection against injury? Ann Surg 2008; 248: 871–879.
8. Daly RC, Topilsky Y, Joyce L, et al. Combined heart and liver transplantation: Protection of the cardiac graft from antibody rejection by initial liver implantation. Transplantation 2013; 95: e2–e4.
9. Olausson M, Mjörnstedt L, Nordén G, et al. Successful combined partial auxiliary liver and kidney transplantation in highly sensitized cross-match positive recipients. Am J Transplant 2007; 7: 130–136.
10. Steen S, Sjöberg T, Pierre L, Liao Q, Eriksson L, Algotsson L. Transplantation of lungs from a non-heart-beating donor. Lancet 2001; 357: 825–829.
11. Steen S, Ingemansson R, Eriksson L, et al. First human transplantation of a nonacceptable donor lung after reconditioning ex vivo. Ann Thorac Surg 2007; 83: 2191–2195.
12. International Randomized Study of the TransMedics Organ Care System (OCS^{TM} Lung) for Lung Preservation and Transplantation (*INSPIRE*). Available at: http://clinicaltrials.gov/ct2/show/NCT01630434?term=Inspire&rank=7. Accessed May 19, 2014.
13. Warnecke G, Wiegmann B, Van Raemdonck D, et al. The INSPIRE international lung trial with the Organ Care System Technology (OCS^{TM}). J Heart Lung Transplant 2013; 32: S16.
14. Van Raemdonck D, Neyrinck A, Cypel M, Keshavjee S. Ex-vivo lung perfusion. Transpl Int 2014; doi: 10.1111/tri.12317 [Epub ahead of print].
15. Cypel M, Yeung JC, Hirayama S, et al. Technique for prolonged normothermic ex vivo lung perfusion. J Heart Lung Transplant 2008; 27: 1319–1325.
16. Cypel M, Rubacha M, Yeung J, et al. Normothermic ex vivo perfusion prevents lung injury compared to extended cold preservation for transplantation. Am J Transplant 2009; 9: 2262–2269.
17. Zych B, Popov AF, Stavri G, et al. Early outcomes of bilateral sequential single lung transplantation after ex-vivo lung evaluation and reconditioning. J Heart Lung Transplant 2012; 31: 274–281.
18. Cypel M, Yeung JC, Machuca T, et al. Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg 2012; 144: 1200–1206.
19. Warnecke C, Moradiellos J, Tudorache I, et al. Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: A pilot study of 12 patients. Lancet 2012; 380: 1851–1858.
20. Wallinder A, Ricksten SE, Silverborn M, et al. Early results in transplantation of initially rejected donor lungs after ex vivo lung perfusion: A case–control study. Eur J Cardiothorac Surg 2014; 45: 40–45.